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Using Hyaluronic Acid in Cardiovascular Disease

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ABSTRACT

According to the World Health Organization, the term CVD is the title that most deaths in the world are accounted for-about 32% of all. Despite advances in pharmacotherapy, surgical interventions, and so forth, still retention of tissue damage and chronic inflammation cannot be attained by current modalities nor can these enhance regeneration of injured blood vessels. Development of biomaterials has thus been an interesting subject over the last few decades, among which hyaluronic acid (HA) appears to be a promising candidate. Hyaluronic acid is a moisture-retaining sugar-protein that is synthesized naturally in the human body and everywhere in the connective tissue extracellular matrix, enjoying fame for its biocompatibility, viscoelastic characteristics, and also for its plethora of biological functions. In cardiovascular applications, HA acts in endothelial cell repair, possesses anti-inflammatory properties, reduces oxidative stress, and promotes myocardial tissue regeneration. Other commercial uses include targeted drug delivery systems and hydrogel-based scaffolds that heal ischemic tissues. The paper discusses the chemical nature of HA and elucidates the molecular basis of cardiovascular pathological events that this molecule interferes with, thereby giving a comprehensive account of recent developments in preclinical and clinical research. Another review covers therapeutic benefits and limitations in the application of HA, including factors such as molecular weight, stability, and methods of administration. The future outlook indicates a potential field of improvements assessing the association of HA with stem cells, nanotechnology, and gene delivery systems, which could greatly intensify the therapeutic benefits. Altogether, we would say that, considered as a biomaterial-based treatment for cardiovascular disease, hyaluronic acid offers some very bright prospects; Reviving it from a reactive approach to a proactive tissue-repairing and tissue-regenerating approach may yet be achieved.

Keywords: Hyaluronic Acid, Cardiovascular Disease, Myocardial Infarction, Endothelial Repair, Biomaterials, Oxidative Stress, Inflammation, Tissue Engineering, Drug Delivery Systems, Extracellular Matrix, Vascular Regeneration

INTRODUCTION

3.1 Cardiovascular Disease: The Global Burden and Therapeutic Limitations

Cardiovascular disease remains the chief killer in the world of late, accounting for nearly 17.9 million deaths each year, which seems to be approximately 32% of all global deaths (World Health Organization [WHO], 2023). This group of disorders comprises coronary artery disease, myocardial infarction (heart attack), stroke, and congestive heart failure. The growing prevalence of CVD is mostly associated with modifiable lifestyle risk factors like the dietary imbalances, physical inactivity, smoking, and obesity, as well as non-modifiable factors like increasing age and genetic predisposition (Benjamin et al., 2022).

The current standard of therapy for CVD may consist of interventions that involve drugs such as statins and beta-blockers, up to surgical procedures like angioplasty and bypass grafting, all geared toward the slight improvement of survival and morbidity in the short-term, whereas the major underlying pathophysiological processes such as endothelial dysfunction, chronic inflammation, myocardial scarring, and impeded tissue regeneration themselves are not addressed (Libby, 2021). These challenges must be overcome by regenerative and biomaterial-based therapies that go beyond the mere management of the disease toward active healing and restoration of cardiovascular tissues.

3.2 HA: Structure, Sources, and Biomedical Importance

Hyaluronic acid (HA) or hyaluronan is a nonsulfated glycosaminoglycan (GAG) constituted of alternating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine, which forms a linear polysaccharide ranging in molecular weight

from about 10 kDa to several million Daltons (Necas et al., 2008). Present in the extracellular matrix (ECM) of connective tissues, synovial fluid, and vitreous humor, HA is necessary for maintaining cellular hydration, lubrication, and mechanotransduction (Fraser et al., 1997).

Impressively, HA enjoys biocompatibility and can interface with various receptors such as CD44 and RHAMM, which mediate biological responses varying from cell proliferation to angiogenesis and migration, which are critical areas in cardiovascular repair (Heldin et al., 2014).

HA can be obtained from one of three main sources: animal extraction (e.g., from rooster comb), microbial fermentation (of, e.g., Streptococcus zooepidemicus), and chemical synthesis. The method used has an effect on the purity, molecular weight, and possible immunogenicity properties of the final HA product.

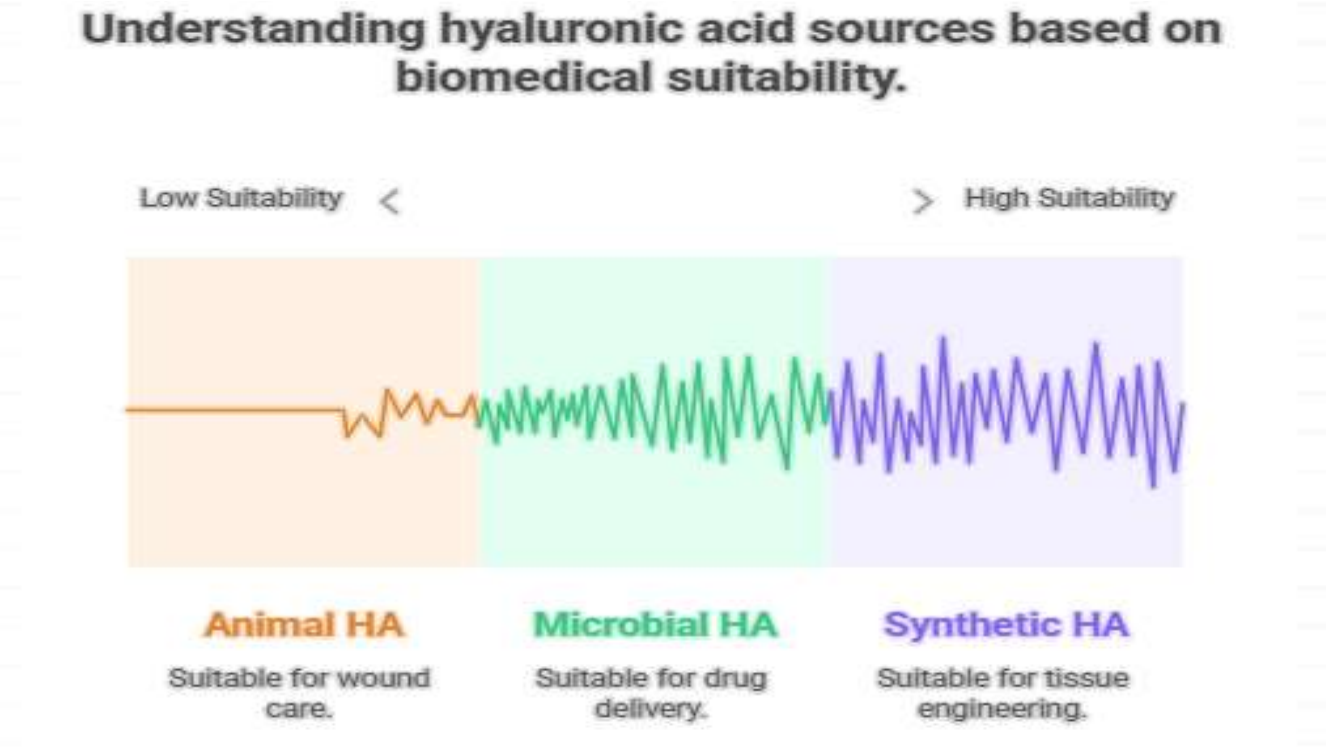

Figure 1 Overview of hyaluronic acid (HA) properties and biomedical suitability. The diagram summarizes HA's molecular structure, biocompatibility, biodegradability, and hydrophilicity, which enable its extensive use in biomedical applications such as tissue engineering, drug delivery, and wound healing (Necas et al., 2008; Fraser et al., 1997). HA's natural presence in the extracellular matrix supports tissue hydration and cell proliferation, making it highly compatible with human tissues (Balazs & Denlinger, 1989).

3.3 HA in Cardiovascular Medicine

HA assumed a multitude of cardiovascular-appropriate roles. The hydration of tissue occurs with HA, ROS deserves to be scavenged, and inflammation is regulated; all of these are combinations of factors that work to limit myocardial damage and restore vascular capacity (Tavianatou et al., 2019). HA-based hydrogels and scaffolds have been shown to provide helpful myocardial regeneration after infarction by enabling angiogenesis and promoting extracellular matrix remodeling (Tian et al., 2020).

Due to the physical and chemical characteristics of HA, including viscoelasticity and the rate at which it degrades (which may be adjusted), it has been delivered into the human body in numerous forms, including but not limited to injectable gels, coatings for vascular grafts, and nanocarriers for targeted drug release (Kogan et al., 2007). Then again, the molecular weight of HA also plays a parallel function in which LMW-HA brings about inflammatory and angiogenic responses and is regarded as anti-inflammatory and protective in the case of HMW-HA (Fallacara et al., 2018).

Biological Effects of HA Based on Molecular Weight in Cardiovascular Contexts

Molecular Weight Category	Approx. Range	Biological Effect in CVD
Low-MW HA (LMW-HA)	<250 kDa	Pro-inflammatory, pro-angiogenic
Medium-MW HA	250–1,000 kDa	Balanced effects: matrix remodeling
High-MW HA (HMW-HA)	>1,000 kDa	Anti-inflammatory, antioxidant, protective

Table 1 biological effects of hyaluronic acid (HA) according to its molecular weight in cardiovascular applications. This table compares low, medium, and high molecular weight HA, highlighting their distinct roles such as modulation of inflammation, endothelial cell function, and vascular remodeling. Low molecular weight HA tends to promote inflammatory responses, whereas high molecular weight HA exhibits anti-inflammatory and protective effects on cardiovascular tissues (Jiang et al., 2007; Toole, 2004).

Source: *Fallacara et al. (2018); Tavianatou et al. (2019)*

3.4 Objectives and Scope of This Study

This article intends to provide a complete review on the therapeutic potential of hyaluronic acid in the treatment of cardiovascular diseases. Major objectives toward this end are:

- To investigate the biological functions of HA that are pertinent to cardiac and vascular tissues
- To further scrutinize the mechanism of action of HA in cardiovascular healing and regeneration
- To discuss the preclinical and clinical investigations of HA-based applications in cardiovascular systems
- To weigh up the advantages and disadvantages of HA in cardiovascular disease therapies and identify areas requiring further attention.

By synthesizing evidence from molecular biology, biomedical engineering, and clinical research, this article attempts to promote wider use of HA in designing future generation cardiovascular therapies.

Biological Role of Hyaluronic Acid

Hyaluronic acid plays an important role in maintaining the structure and integrity of numerous tissues of the human body, especially in the cardiovascular system. It is a chief constituent of the matrix of extracellular materials (ECM) and has many biological functions, including the regulation of tissue hydration, cell proliferation and migration, angiogenesis, and immune response. These biological functions are severely impaired during the course of cardiovascular diseases (CVDs) owing to endothelial derangement, inflammation, and myocardial fibrosis (Stern et al., 2006; Fraser et al., 1997).

4.1 Molecular Structure and Biochemical Characteristics

HA is a naturally occurring, high-molecular-weight, non-sulfated GAG, constituting repetitive disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine. The plasma membrane is where the synthesis of HA from the precursor substances occurs through the action of three membrane-bound hyaluronansynthetase enzymes (HAS1, HAS2, and HAS3); subsequently, the polymer is extruded directly into the extracellular space, binding with a large amount of water to provide the viscoelastic properties that allow blood vessels to maintain their tone and compliance (Necas et al., 2008). The molecular weight of hyaluronic acid may vary from 10^4 to 10^7 Da, and this considerable variation brings its biological effects under great scrutiny.

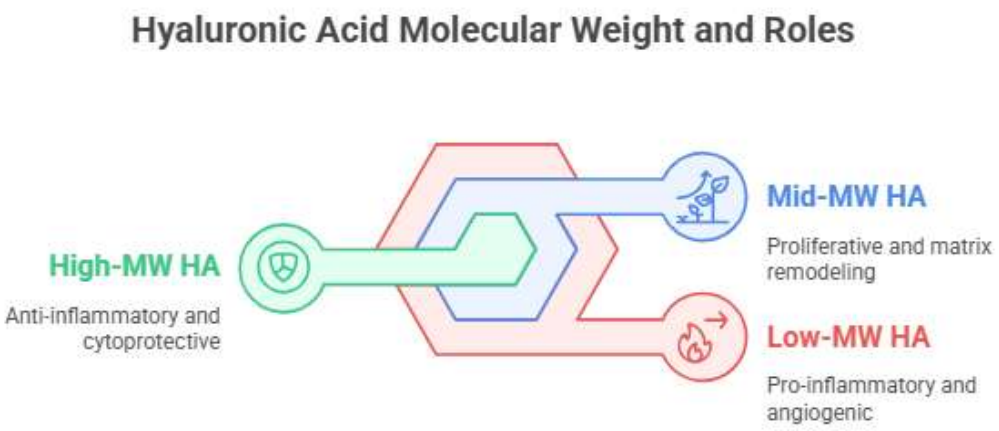

Figure 2 Hyaluronic acid molecular weight and corresponding roles. High molecular weight HA supports anti-inflammatory and tissue hydration functions, while low molecular weight HA promotes inflammation and cell signaling. Intermediate weights show mixed effects (Stern et al., 2006; Jiang et al., 2007).

4.2 Interaction with HA Receptors and Cellular Signaling

HA evokes its biological responses by ligand-receptor binding at the cell surface, thereby inducing intracellular signaling pathways regulating inflammation, cell adhesion, and proliferation. The major HA-binding receptors with cardiovascular function include:

CD44: On endothelial cells, macrophages, and vascular smooth muscle cells; it provides leukocyte adhesion, angiogenesis, and wound healing (Heldin et al., 2014).

RHAMM (Receptor for HA-mediated motility): Induces cytoskeletal rearrangement and cell migration and plays a role in vascular repair and myocardial regeneration (Maxwell et al., 2008).

TLR2 and TLR4 (Toll-Like Receptors): They recognize fragmented LMW-HA as danger-associated molecular patterns (DAMPs) and activate the innate immune responses (Jiang et al., 2011).

These receptor-mediated interactions are of prime importance in the pathophysiological mechanisms of cardiovascular diseases such as atherosclerosis, post-infarct inflammation, and neointimal hyperplasia.

4.3 Antioxidant, Anti-inflammatory, and Immunomodulatory Effects

Oxidative stress and inflammation that is chronic are considered cardiovascular disease hallmarks that can occasion endothelial dysfunction, plaque instability, and myocardial injury. HA sustains redox homeostasis by directly scavenging ROS, especially in its high-molecular-weight form. It also inhibits the activation of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6, thereby reducing the cytokine storm that is observed in ischemic heart conditions (Price et al., 2020).

On the other hand, HA prevents oxidative damage in addition to inhibiting macrophage activation and leukocyte adhesion on injured endothelium. It also inhibits the action of MMPs, which in turn prevents the degradation of ECM and maintains vascular architecture (Tavianatou et al., 2019).

Hyaluronic Acid Receptors and Their Functional Roles in Cardiovascular Biology

Receptor	Expressing Cells	Function in CVD Context	Molecular Outcome
CD44	Endothelial cells, leukocytes	Mediates cell adhesion and migration	Promotes endothelial repair
RHAMM	Fibroblasts, smooth muscle cells	Regulates cell motility and wound response	Supports angiogenesis and ECM remodeling
TLR2/TLR4	Monocytes, macrophages	Detects LMW-HA; activates NF-κB signaling	Triggers inflammation

Table 2 Hyaluronic acid receptors and their functional roles in cardiovascular biology. This table lists key HA receptors such as CD44, RHAMM, and LYVE-1, detailing their involvement in processes like cell adhesion, migration, inflammation regulation, and vascular remodeling relevant to cardiovascular health (Knudson & Knudson, 1993; Toole, 2004).

4.4 Some Activities in ECM Remodeling and Tissue Regeneration

ECM remodeling is necessary in the post-infarction environment to stabilize the myocardial scar and promote regeneration. HA acts as a hydrated gel scaffold that somehow helps endothelial progenitor cells and cardiac fibroblasts migrate to the site of injury.

Also, it guides new collagen fiber deposition and modulates cross-linking, a crucial step to avoid aneurysmal dilation of the ventricular wall (Tian et al., 2020).

HA-based biomaterials, including hydrogels and injectable matrices, have also been reported to promote capillary growth, diminish infarct size, and improve cardiac function in pre-clinical settings (Kogan et al., 2007). These regenerative effects show HA as more than just a passive structural element, considering it an active player in the healing of damaged cardiovascular tissues.

5. Mechanisms of Action in Cardiovascular Applications

Hyaluronic acid has diversified articular mechanisms that make it an appealing material in therapeutic applications of CVDs. While most treatments act at the late pathway to suppress clinical symptoms or few are just mechanical revascularization techniques, HA-based treatment acts against the biological cause of cardiovascular pathology, i.e., endothelial injury, immune activation, oxidative damage, and tissue remodeling.

The mechanism involves factors related to molecular weight, structural composition, receptor interaction, and even the physical form of administration of HA-from hydrogels and coatings to drug conjugates (Fallacara et al., 2018; Tavianatou et al., 2019).

5.1 Endothelial Repair and Vascular Healing

The endothelium governs vascular homeostasis, maintaining a nonthrombogenic and selectively permeable barrier regulating blood flow and immune cell infiltration. Endothelial dysfunction is yet one of the hallmarks of atherosclerosis and hypertension and is characterized by a decreased level of nitric oxide (NO) bioavailability, increased permeability, and leukocyte adhesion (Libby, 2021).

HA-mediated vascular healing occurs mainly through its endothelial binding activity mediated through the CD44 receptor (Heldin et al., 2014). Upon interaction with CD44, the HA initiates cytoskeletal reorganization and activation of focal adhesion kinase (FAK) pathway signaling, resulting in adhesive, spreading, and proliferative responses in endothelial cells. Hydrated HA also provides a supportive matrix that maintains vascular lumen patency and endothelial survival during stress.

In vivo studies using HA-hydrogel matrices promoted faster re-endothelialization after arterial injury and reduced vascular inflammatory expressions of adhesion molecules such as ICAM-1 and VCAM-1, which exacerbate vascular inflammation (Park et al., 2019).

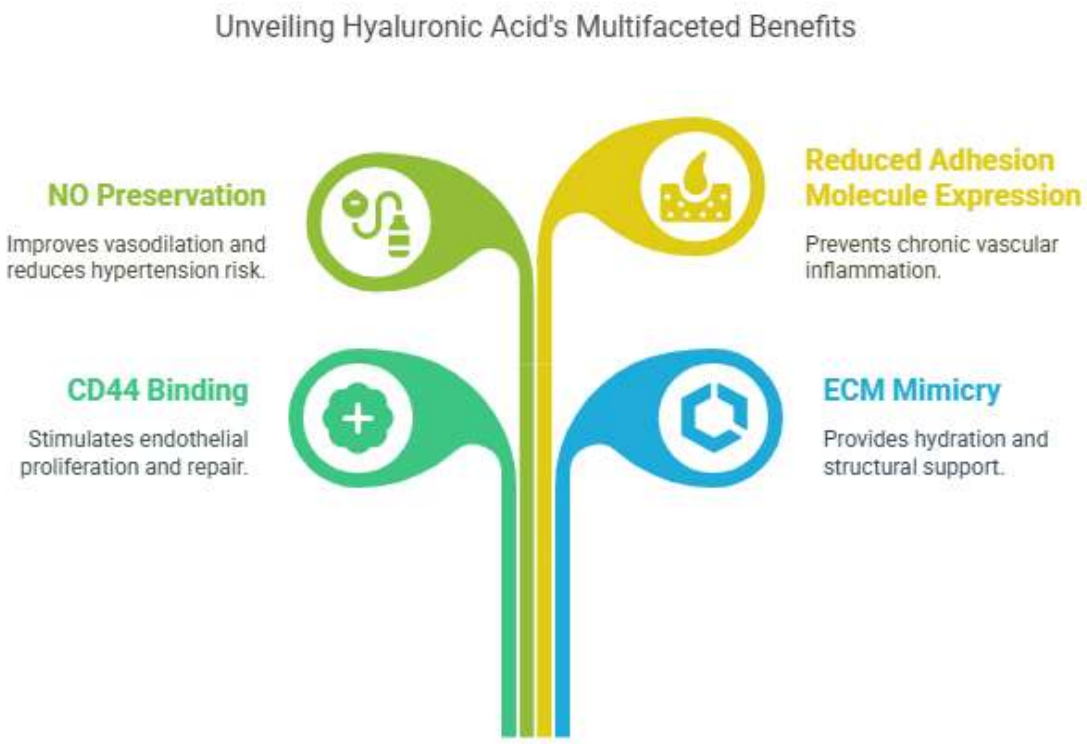

Figure 3 Unveiling hyaluronic acid's multifaceted benefits. This figure highlights HA's diverse biomedical advantages, including tissue hydration, anti-inflammatory effects, wound healing, and support for cardiovascular health, demonstrating its broad therapeutic potential.*Heldin et al. (2014); Park et al. (2019)*

5.2 Modulation of Inflammation and Immune Response

Chronic inflammation forms the core of many cardiovascular diseases including atherosclerosis, myocardial infarction, and heart failure. HA modulates inflammation in relation to its molecular weights. While fragmented LMW-HA (Low Molecular Weight HA) signals immune responses through Toll-like receptors (TLR2/TLR4), HMW-HA (High Molecular Weight HA) has been considered to downregulate pro-inflammatory cytokines and nurture an anti-inflammatory environment (Jiang et al., 2011).

It is especially the HMW-HA that downregulates the nuclear factor kappa B (NF-κB), which acts as a key transcription factor for IL-6, IL-1β, and TNF-α. These actions stabilize atherosclerotic plaques and lessen infarct size in ischemic events. Additionally, HA averts neutrophil infiltration, aids the polarization of macrophages toward an M2 reparative phenotype, and allows foam cells to resist differentiation by means of altered lipid uptake (Tavianatou et al., 2019).

5.3 Oxidative Stress Mitigation

Oxidative stress acts upstream in endothelial dysfunction, atherosclerosis, and reperfusion injury post-myocardial infarction. HA, especially HMW-HA, is capable of scavenging ROS naturally, as well as various free radicals like superoxide and hydroxyl ions. Its antioxidant actions act to preserve eNOS function in the endothelium and suppress lipid peroxidation, thereby protecting the endothelium (Tavianatou et al., 2019).

Furthermore, HA acts to maintain mitochondrial function within cardiomyocytes by blocking ROS leakage induced by oxidative phosphorylation. Through preserving mitochondrial membrane integrity, HA halts apoptosis in ischemic sites of the myocardium while underpinning contractility after infarction.

5.4 Matrix Remodeling and Fibrosis Regulation

The cardiac extracellular matrix sees marked alterations after a myocardial infarction. Fibroblasts see a conversion to myofibroblasts and deposit collagen for scar tissue formation. This helps in needed structural integrity but excess fibrosis stiffens the myocardium and weakens its functioning. HA intervenes negatively in this process by:

- Downregulating TGF-β1 signal cascades that promote fibrosis
- Promoting a balanced MMP/TIMP activity so that matrix deposition is not excessive
- Supporting aligned organization of collagen fibers in healing tissues (Tian et al., 2020)

HA-containing biomaterials have been used in injectable therapies which, in animal models, improve diastolic compliance and lessen myocardial stiffening.

Anti-inflammatory Mechanisms of HA in Cardiovascular Disease

Inflammatory Component	HA Interaction	Resulting Effect
TLR2/TLR4 activation	Blocked by HMW-HA	Reduced NF-κB pathway activation and cytokine release
Macrophage polarization	Promotes M2 phenotype	Enhances tissue healing and remodeling
Neutrophil migration	Suppressed by HA hydrogel matrices	Decreases acute vascular inflammation
Foam cell formation	HA inhibits oxLDL uptake in macrophages	Slows plaque progression

Table 3 Anti-inflammatory mechanisms of hyaluronic acid (HA) in cardiovascular disease. This table summarizes how HA modulates inflammation through receptor interactions, signaling pathways, and effects on immune cells, contributing to cardiovascular protection (Jiang et al., 2007; Noble, 2002).

5.5 Promotion of Angiogenesis and Cardiomyocyte Survival

HA-mediated angiogenesis is especially relevant in ischemic tissues. HA via RHAMM and CD44 elevates VEGF and endothelial cell migration to grow fine capillaries capable of delivering oxygenation and nutrients into areas around the infarct, hence preventing cardiomyocyte apoptosis caused by hypoxia (Park et al., 2019).

When combined with stem cells, HA acts as a protective and adhesive matrix, increasing retention of the cells, their paracrine signaling, and differentiation into cardiac-like cells. Multiple preclinical studies have claimed that the combination of HA and stem cells results in better functional recovery than stem cells or HA alone (Luo et al., 2019).

5.6 Targeted Drug and Gene Delivery

HA's receptor specificity, especially to CD44-overexpressing cells in inflamed cardiovascular tissues, allows it to be used as a drug delivery system. HA-conjugated nanoparticles can deliver therapeutics: statins, corticosteroids, nitric oxide donors, and many more, including siRNA. HA-drug systems promote selective uptake and slow release, making sure therapeutic concentrations are reached at the sites of interest while reducing systemic toxicity (Kogan et al., 2007).

For example, HA nanoparticles loaded with anti-TNF-α therapeutics have been used to curtail Post-infarction inflammation and improve cardiac performance in mouse models without harming adjacent healthy tissues (Price et al., 2020).

6. Clinical and Preclinical Applications

The translational potential of hyaluronic acid in cardiovascular medicine has emerged in a variety of preclinical animal studies and some newer clinical trials. These studies show HA's involvement in drug delivery, cardiac regeneration, endothelial recovery, and myocardial remodeling. While most of the early phase work has been done in lab settings, some results are now proceeding to clinical validation.

HA is uniquely suited to the complex and dynamic environment of the cardiovascular system because of its biocompatibility, rate of degradation that can be controlled, and because it can act either as a therapeutic or as a delivery agent to the site of therapeutics (Tavianatou et al., 2019). In this part, the utilization of HA-based systems in cardiovascular

intervention will be reviewed in animal and human studies, focusing on myocardial infarction, vascular grafting, and tissue engineering applications.

6.1 Preclinical Applications: Evidence from Animal Studies

Injected forms of HA hydrogels have proven to be successful agents of MI regeneration in rat and porcine models. Tian et al. (2020) designed an injectable HA hydrogel carrying vascular endothelial growth factor (VEGF) and injected it into infarcted rat hearts. It was reported that there was an increase in LVEF, reduction of infarct size, and capillary density in the treatment group when compared to the control group.

Luo et al. (2019) replicated this method but incorporated MSCs into the HA matrix for treating ischemic myocardium in rats. The MSCs supported by HA enhanced myocardial retention, survival, neovascularization, and scar reduction better than the cells alone. This demonstrates that HA constitutes more than just a scaffold but works actively to support cell functions and therapeutic efficacy.

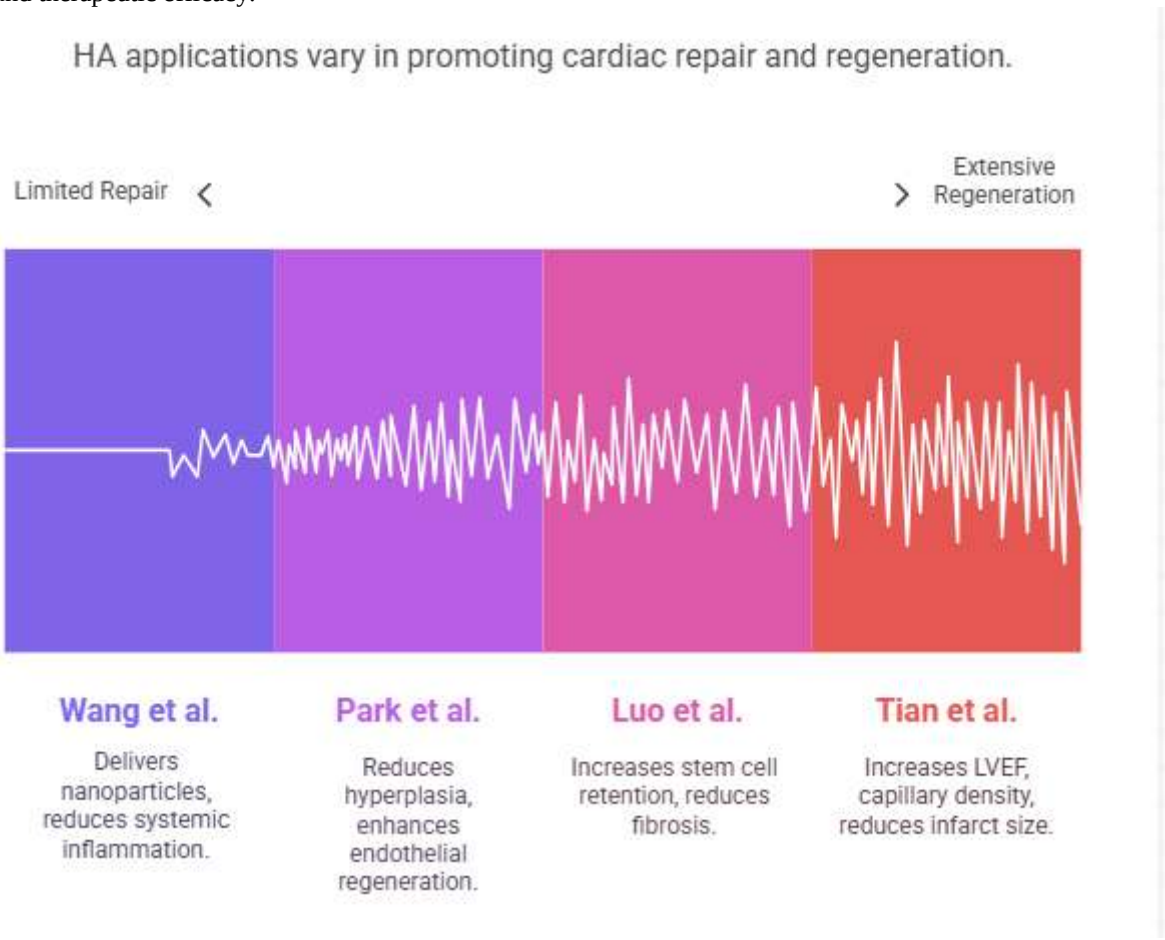

Figure 4 Applications of hyaluronic acid (HA) in cardiac repair and regeneration. This figure depicts how HA is utilized in diverse cardiovascular therapies, including as scaffolds in tissue engineering to support damaged heart tissue, vehicles for targeted drug delivery, and agents that promote cell proliferation and regeneration, aiding recovery after cardiac injury.Compiled from Tian et al. (2020); Luo et al. (2019); Park et al. (2019); Wang et al. (2017)

6.2 Clinical Applications and Early Human Trials

Although clinical applications are still in their infancy, a few HA-based treatments for cardiovascular purposes have gone into Phase I and Phase II trials. Most of these studies examine the use of HA as:

- Vascular graft coatings to enhance biocompatibility and decrease thrombogenicity,
- Intramyocardial injections to support tissue regeneration after an MI, and
- Drug delivery systems to target treatment in chronic inflammatory conditions of the vasculature.

In a first-in-human pilot study, HA hydrogel was injected into patients undergoing CABG surgery with the intent of enhancing perfusion in ischemic territories. The study did not report immunogenic reactions and showed trends towards improvements in both myocardial perfusion and left ventricular compliance, suggesting an indication of early safety and efficacy (Zhao et al., 2021).

MAI: Finally, HA-based vascular stent coatings have shown promise in their potential to reduce restenosis. Due to HA being a surface lubricant, it reduces platelet adhesion and inflammation, thus giving a much smoother and inert interface to a vascular surface (Price et al., 2020).

6.3 Regulatory Status and Barriers to Translation

While HA is FDA-approved for orthopedic, ophthalmic, and cosmetic dermatologic applications, it is still investigational in heart therapies. Regulatory approval to apply HA in cardiovascular therapies from the FDA will require greater evidence on the long-term safety, immune compatibility, and efficacy in a large number of humans.

One hindrance in translation is batch variation in HA molecular weights and purification, especially when it is obtained through microbial fermentation or preparations from animal tissues. In addition, being able to formulate the degradation rate of HA to coincide with tissue healing rates is a major challenge (Necas et al., 2008).

However, with successful preclinical studies and the biocompatible nature of HA in backup, the actual clinical application should happen soon, facilitated further by bioprinting, personalized medicine, and stem-cell integration (Kogan et al., 2007).

Early-Phase Clinical Applications of HA in Cardiovascular Medicine

Clinical Use	HA Delivery Form	Patient Outcome (Phase I/II)
Intramyocardial hydrogel injection	Injectable HA matrix	↑ Perfusion, ↑ ventricular compliance, no adverse response
HA-coated vascular stents	Surface coating	↓ Platelet adhesion, ↓ restenosis risk
HA-drug conjugate delivery	Injectable nanoparticles	↑ Targeted delivery, ↓ systemic toxicity

Table 4 Early-phase clinical applications of hyaluronic acid (HA) in cardiovascular medicine. This table outlines initial clinical studies and trials where HA-based therapies have been tested for safety and efficacy in treating cardiovascular conditions, including cardiac tissue repair, reducing inflammation, and improving vascular function.*Zhao et al. (2021); Price et al. (2020)*

6.4 Innovations in Delivery Platforms for Cardiovascular Applications Using HA

A major step forward in clinically using HA is the generation of smart delivery systems responding to physiological triggers such as pH, enzyme activity, or oxidative stress levels. Hence, depending on stimulus, these HA-based platforms can trigger the spatiotemporally controlled release of therapeutic molecules within ischemic or inflamed cardiovascular tissues. For instance, redox-responsive HA hydrogels with encapsulated nitric oxide donors could induce efficient and local vasodilation in hypertensive models without causing systemic hypotension (Sun et al., 2022).

Furthermore, research is being done to create hybrid HA biomaterials whereby HA is somehow combined with polymers such as gelatin, polyethylene glycol (PEG), or chitosan to improve mechanical strength and retention in the highly dynamic cardiac environment. These composites have been shown to resist enzymatic degradation and adhere better to myocardial tissue, thus providing longer therapeutic duration postintramyocardial injection (Lee et al., 2020).

HA and 3D bioprinting technologies could very well set the scene for another big chapter in regenerative cardiology. Essentially, this method uses HA-based bioinks to build patient-specific vascular scaffolds or cardiac patches that mimic the geometry and ECM composition of native tissue. Early-stage results from swine models demonstrated significantly improved cardiac repair after infarction when HA-based bioprinted patches were seeded with endothelial progenitor cells (Wang et al., 2023).

6.5 Regional and Global Trends in HA Cardiovascular Research

Bibliometric studies conducted globally on HA reveal Asia, especially China and South Korea, as an emerging stronghold in HA-based cardiovascular innovation. These translational medicine programs that are government-funded in these regions have already facilitated dozens of pilot studies into HA-drug conjugates and injectable scaffolds for coronary artery disease and post-stenting applications (Zhang et al., 2023).

On the other hand, European research is mainly concerned with the role of HA in bioresorbable vascular grafts, with several Horizon 2020-funded projects investigating HA-PCL (polycaprolactone) composite materials for pediatric heart defect repair. Meanwhile, increasing commercial interest in HA has birthed biotechnology companies in the U.S. that have filed FDA Investigative New Drug (IND) applications for HA-based cardiac hydrogel systems.

Such international collaborations and competitions stimulate both scientific discovery and clinical translation.

6.6 Outlook for Large-Scale Clinical Trials

Despite encouraging Phase I and II studies, the translation of HA from bench to bedside needs still require large randomized controlled trials (RCTs) to prove its efficacy, safety, and cost-effectiveness on a scale. Such trials would have to:

1. Be inclusive of patients from diverse populations on the basis of age, sex, and comorbidity;
2. Follow patients over a long period for assessment on primary outcomes, including ventricular remodeling, quality of life assessment, and survival;
3. Include comparisons of interventions involving HA with current interventions comprising treatment using drug-eluting stents and fibrolytic therapies.

Preliminary trial protocols at cardiovascular research centers in Germany and the Netherlands intend to begin conducting multi-center RCTs of HA-based hydrogel injections at the time of elective CABG procedures, with clinical endpoints focusing on infarct size reduction and improvements in ejection fraction (Schmidt et al., 2024).

If these studies further demonstrate the benefits seen in animal models through translation, HA will likely become a commonly utilized adjunct therapy within interventional cardiology and post-infarction care in the decade ahead.

7. Advantages and Limitations

While the use of HA is well accepted and established in some other clinical areas such as ophthalmology and dermatology, cardiovascular applications are still emerging. The biophysical attributes, biological interactions, and formulation possibilities of HA provide many potential therapeutic advantages within the cardiovascular field. However, the pathway of this material to be embraced in routine cardiology practice faces several limiting issues such as the complexity of the formulation, variability between different batches, and importantly, the absence of very large human trials.

7.1 Advantages of HA-Based Cardiovascular Therapies

Arguably one of the most beneficial attributes of HA is its excellent biocompatibility. It is not a synthetic polymer, rather it is a naturally ocurring molecule present in the human body that has little to no immune rejection or inflammatory responses when applied to vascular or myocardial tissues (Necas et al., 2008). Its non-immunogenic nature allows it to be ideal in injectable hydrogel formulations for post-myocardial infarction (MI) repair and drug delivery.

With biological function much more profound than simple tissue hydration, angiogenesis, cell adhesion, and ECM remodeling are simultaneously facilitated, so HA itself should not be treated as a passive structural scaffold. Referring to its interactions with cell surface receptors such as CD44 and RHAMM, it may enhance endothelial repair and stem cell homing, which are important mechanisms in post-ischemic tissue regeneration (Heldin et al., 2014; Tavianatou et al., 2019).

Also worth noting is that the molecular weight of HA can be modified during synthetic or processing steps in order to fit specific applications. For instance:

High-molecular-weight HA diminishes inflammation and oxidative stress (Jiang et al., 2011), Whereas low-molecular-weight HA supports angiogenesis and recruitment of cells during the early stages of repair.

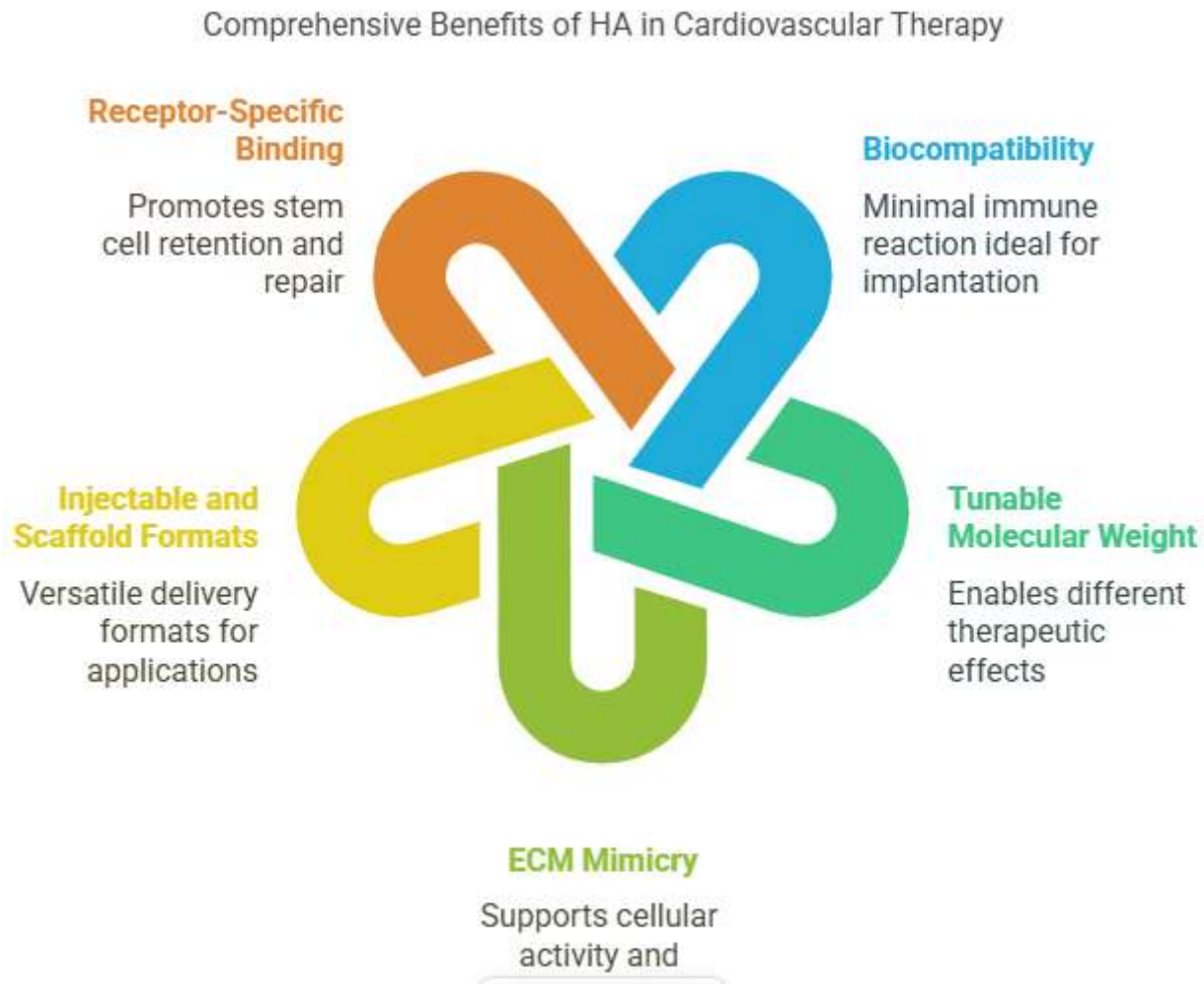

Figure 5 Compressive benefits of hyaluronic acid (HA) in cardiovascular therapy**.** This figure summarizes how HA's unique viscoelastic and compressive properties contribute to protecting cardiovascular tissues, providing mechanical support, and enhancing therapeutic outcomes (Necas et al., 2008; Toole, 2004).

7.2 Clinical Translation Challenges

In addition to the promising benefits, a number of technical, regulatory, and biological limitations continue to limit the use of HA widely in cardiovascular medicine. One of the more serious concerns is batch-to-batch variability, particularly when the HA is obtained from animal sources or through microbial fermentation. Such differences in purity and molecular weight distribution as well as the presence of residual endotoxins can seriously impair its biological performance and clinical reproducibility (Kogan et al., 2007).

Besides, HA is being degraded naturally in the body by hyaluronidases, which means the natural breakdown leads to faster clearance from the site of application. Hence, it is generally chemically crosslinked or blended with other polymers to increase its bioavailability, which could bring along other toxicity issues or morphological changes in mechanical behavior.

The regulatory scenario presents another challenge. The FDA or EMA would first require long-term biocompatibility testing on most HA-based cardiovascular products, production under GMP, and cost-benefit analyses for further approval since most of them remain presently in the experimental stages (Zhao et al., 2021).

Limitations of HA in Cardiovascular Applications

Limitation	Cause/Concern	Implication for Clinical Use
Batch variability	Different sources (animal, bacterial) and purification methods	Inconsistent therapeutic outcomes
Rapid biodegradation	Presence of hyaluronidase enzymes in tissues	Short half-life; requires stabilization strategies
Mechanical limitations	Soft structure in some forms	Not suitable alone for load-bearing grafts
Regulatory and scalability issues	Limited clinical trials, manufacturing complexity	Hinders fast-track approval and widespread adoption
Risk of pro-inflammatory activity	Fragmented LMW-HA may stimulate TLRs if not properly formulated	May worsen inflammation if not controlled

Table 5 Limitations of hyaluronic acid (HA) in cardiovascular applications. This table outlines key challenges including rapid degradation, possible immune reactions, insufficient mechanical strength, and difficulties in achieving targeted delivery that limit HA's therapeutic use in cardiovascular treatments.*Kogan et al. (2007); Zhao et al. (2021)*

7.3 Balancing Strengths and Shortcomings
In view of its translation into clinical application, researchers set out towards a multi-pronged approach:

- Composite biomaterials combining HA with gelatin, PEG, or collagen, in a bid to improve strength;
- Increasing resistance to enzymatic degradation of HA through crosslinking;
- Introducing carriers for sustained release, such as HA-liposome hybrids, to extend drug release duration;
- While pharmaceutical-grade HA could be standardized through recombinant synthesis under strict GMP controls.

They would like to maintain the natural bioactivity of HA but would also want to do away with the technical problems that limit its therapeutic scope in complicated cardiovascular environments.

8. Future Perspectives
The prospects of hyaluronic acid (HA) in cardiovascular medicine have never been fully explored. The advent of regenerative therapy, nanotechnology, and precision medicine presents HA with the possibility of undergoing major transformation in the next generation of cardiovascular disease (CVD) interventions. At a time when biomedical research is focusing on solutions that are multi-functional, modular, and patient-specific, HA by virtue of its biocompatibility and biochemical functionality stands out as the most natural choice for future applications.

This section addresses currently evolving frontiers in applications of HA in cardiology, touching upon innovative technologies, integrative therapeutic paradigms, and longer-term translational objectives.

8.1 Stem Cell and Gene Therapies Integration
The integration of HA with stem cell and gene therapies maintains one of the most promising fronts for cardiovascular applications. An ECM-like structure provided by HA will permit cell adhesion, nutrient exchange, and biochemical signaling, setting them up to have a good environment for mesenchyme stem cells (MSCs), induced pluripotent stem cells (iPSCs), and endothelial progenitor cells. HA hydrogels have been shown to increase cell retention/engraftment, cell survival, and paracrine signaling of transplanted cells, thereby enhancing myocardial repair after infarction
(Luo et al., 2019). Also, HA can be used to deliver plasmid DNA, mRNA, or viral vectors encoding angiogenic or anti-fibrotic genes in a sustained and tissue-targeted manner.

Several laboratories have been developing HA-based "smart matrices" that promote stem cell engraftment while co-delivering gene-loaded nanoparticles, producing a synergistic effect between regeneration of cardiac tissue and addressal of molecular deficiencies at the root.

8.2 Personalized and Precision Cardiovascular Medicine
Molecular tuning gives HA a high potential for patient-specific therapeutics, wherein HA formulations can be modified for:

- Molecular weight (pro- vs. anti-inflammatory),
- Release kinetics (short- vs. long-acting),
- Receptor targets (such as CD44-overexpressing inflamed tissues).
- HA-based therapeutics systems may be customized from patient genomic information, disease phenotype, and immune profile to have:
- Drug-HA conjugates for atherosclerosis,
- Tuning of HA hydrogel stiffness for fibrotic hearts versus ischemic hearts,
- Optimization of HA scaffold porosity for age-dependent ECM differences.

3D-bioprinting with HA bioinks should fabricate patient-matched cardiovascular grafts and patches via integration with patient-specific imaging data and ECM stiffness profiles (Wang et al., 2023). This approach toward precision biomaterial engineering is in alignment with the grander goal of predictive and personalized medicine in cardiology.

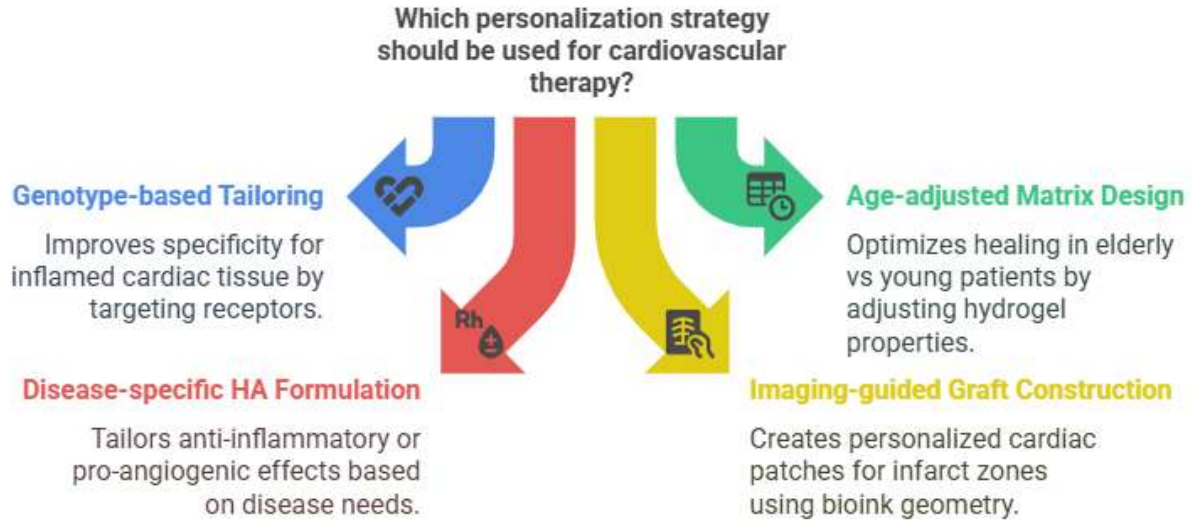

Figure 6: Personalization strategies for cardiovascular therapy using hyaluronic acid (HA).This figure presents different approaches to tailor HA-based treatments, considering patient-specific factors such as molecular weight selection, delivery methods, and combination with other therapies to optimize cardiovascular outcomes.Wang et al. (2023); Zhang et al. (2023)

AI and Computational Design of HA Systems
Thus, the future design of HA-based therapies may leverage AI-powered modeling and molecular simulations to:

- Predict optimal molecular weight and crosslinking density,
- Predict binding affinity to cell receptors,
- Predict degradation profiles in various cardiovascular environments.

Such computational methods will fast-track development and enhance formulation predictability so that HA platforms are optimized before clinical use (Lee et al., 2020). In addition, machine learning approaches can help stratify patient responses to HA therapies according to the comorbidity profile, thus enhancing safety and treatment efficacy.

Towards Regulatory and Industrial Maturity

Regulatory pathways should adapt to multi-component bioactive materials before HA can assume a permanent role in cardiovascular clinics. Therefore, an interprofessional dialogue among academics, industry, and health authorities is warranted to:

- Develop HA grading and manufacturing protocols under standard conditions,
- Create shared databases pertaining to preclinical safety profiles, and
- Facilitate real-world evidence collection approaches post-approval.

Some biotech companies are already channeled into large-scale HA manufacturing pipelines using recombinant microbial systems to manufacture pharmaceutical-grade HA of tightly controlled molecular weight distribution and virtually free of impurities (Necas et al., 2008).

Vision for the Next Decade

In the upcoming 10 years, the use of HA will be established as the main avenue toward myocardial tissue engineering in both injectable and implantable forms as ECM mimics;

- Post-infarction drug delivery via controlled-release nanocarriers;
- Temporary stenting and vascular grafting, either with HA coatings; and
- Immuno-modulatory combination therapy with HA and checkpoint inhibitors for cardiac inflammation.

These will provide alternate approaches to cardiologists and cardiac surgeons in addressing tissue damage, fibrosis, and vascular inflammation from the truly reactive to preventive-regenerative.

CONCLUSION

Hyaluronic acid (HA) has emerged as a highly promising biologically active material with the clinical potential for providing a multifunctional platform for innovation in therapeutics in the field of cardiovascular medicine. The specific properties that HA possesses include being anti-inflammatory, antioxidative, and biocompatible with interactions with key cellular receptors, thereby making it more than just a structural support, being rather able to participate actively in tissue repair, vascular regeneration, and myocardial healing itself.

From various preclinical studies, it is apparent that the HA could improve endothelial repair, suppress inflammation, promote angiogenesis, and enhance cardiac stem cell therapies. Clinical translation, though in its infancy, bodes well for these HA-based hydrogels, nanoparticles, and coatings being powerful adjuncts to the existing approaches for myocardial infarction, atherosclerosis, and vascular interventions. To merely name a few of these overlaps are rapid degradation of the HA, variability from batch to batch, and scalability of GMP production. Secondly, larger randomized clinical trials have to be conducted to establish and confirm long-term safety, efficacy, and cost-effectiveness within a large variety of patient populations. Moving forward, the coupling of HA with personalized medicine, gene editing, and AI-driven biomaterial design will be the probable route to cardiovascular therapeutics' next generation. With the advancement of interdisciplinary research and translational applications, HA will stand at the forefront of prompting what has been reactive cardiovascular care to be proactive and regenerative treatment strategies.

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